REMARKS

Claim 1 has been cancelled, claims 6-8 and 25 have been amended, and claim 32 has been withdrawn. Accordingly, claims 6-8, 25, 26, and 28-31 are currently under examination.

Examiner Interview

The undersigned attorney wishes to thank Examiner Clow for the courtesies extended to the applicants' representatives, the undersigned and Andrew Serafini, during the telephonic interview conducted March 26, 2008. During the interview the participants discussed the issues raised in the office action of December 28, 2007, specifically the Takasaki *et al.* reference in relation to the pending rejection under 35 U.S.C. § 103.

Rejection under 35 U.S.C. § 103

Claims 6-8, 25, 26, and 28-31 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over the DOCK 4.0 User's Guide (1998) in further view of Takasaki et al. (Nature Biotechnology (1997) Vol. 15: pages 1266-1270). The examiner asserts that the DOCK 4.0 User's Guide discloses a program with which the user could ascertain certain physical characteristics of a site of interest, particularly ligand-binding and active sites, but does not disclose identifying a compound that binds to a cavity or allosteric cavity and modulates intermolecular interactions between a functionally critical site of a target protein and a modifier. According to the examiner, Takasaki allegedly discloses identifying a compound that binds to a "site that is different from the authentic receptor" – which applicants understand the examiner to mean a site distinct from the "critical site" – and modulate the interaction between the critical site of the TNF-α receptor and its modifier TNF-α. Consequently, the examiner believes that the combination of the DOCK User's Guide and Takasaki render the claims obvious. Applicants respectfully disagree with some of the examiner's factual characterizations of the cited art. A proper understanding of the substance of this art shows that these references do not disclose every element of the claims, and therefore do not render the claims unpatentable.

With respect to the teachings and suggestions in the DOCK User's Guide, applicants agree that it does not disclose identifying a compound that binds to a cavity or allosteric cavity and modulates intermolecular interactions between a functionally critical site of a target protein and a modifier. Further, the DOCK User's Guide does not disclose characterizing the binding site of compound that modulates (in claims 6-8, and 25) or an allosteric modulator (in claims 26, 28-31), but instead teaches characterizing the binding site of a modifier (or ligand). *See, e.g.*, DOCK User's Guide, at 11, 19-27. Applicants define "modifier" as a compound which is involved in the intermolecular interaction with the target protein and is "used interchangeably herein with the term 'ligand.'" Specification at page 7, lines 6-19. Moreover, Applicants note that cavity or allosteric cavity that is distinct from the critical site or ligand-binding site. Specification at 9, lines 1-11. Accordingly, the DOCK User's Guide does not teach or suggest either: (a) characterizing the cavity or allosteric cavity bound by the compound that modulates or an allosteric modulator, respectively, or (b) a compound that binds to a cavity or allosteric cavity and modulates intermolecular interactions between a functionally critical site of a target protein and a modifier.

The Takasaki reference does not fill any of the gaps in the teachings or suggestions of the DOCK User's Guide. The examiner asserts that the site characterized in Takasaki is "different from the authentic receptor" and sites page 1269, col. 1. Applicants presume that the examiner means that the Takasaki is characterizing an allosteric site on the receptor that is not a critical site on the receptor (i.e., the site at which the ligand binds to the receptor). Applicants respectfully submit that the examiner misinterprets the Takasaki reference.

The Takasaki reference does not teach or suggest identifying an allosteric site on the receptor. Rather, Takasaki relates to interactions that occur at one of the critical sites –WP9– on the TNF receptor where its ligand TNFα binds. Specifically, they designed peptidomimetics having a similar shape to this critical site and an anti-TNFα monoclonal antibody, which would have the ability to bind TNFα, and tested whether the peptidometic prevented TNFα binding and activation of the receptor. Takasaki states that the peptidomimetics "work in a novel way by binding to and disrupting or disabling the TNFα trimer therby preventing is effective interaction with its cognate receptor." page 1266, col. 2; *see* also page 1269, col. 1 ("peptidomimetics bind TNFα and either block the [receptor] complex formation or form a weaker unstable receptor-binding complex."). Applicants point

that this understanding of Takasaki is consistent with the preliminary section of Example 1. Specification, at 16-17. Example 1 extends these preliminary studies by describing a cavity close to the WP9 binding site on the receptor and screening compounds to determine whether they elicit an allosteric effect on the receptor function via binding the cavity. *Id.*; Figure 2. Thus, Takasaki does not teach or suggest identifying compounds that bind to an to a cavity or allosteric cavity and modulates intermolecular interactions between a functionally critical site of a target protein and a modifier.

As the DOCK User's Guide and Takasaki fail to teach or suggest every limitation of the claimed invention, applicants respectfully request withdrawal of the rejection.

Conclusion

Favorable consideration and an early notice of allowance are earnestly solicited. If the examiner believes that a telephone conversation would further the prosecution of this case, she is invited to telephone the undersigned at her convenience.

Date: March 28, 2008

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